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Exercise works for depression: Building the bridge between clinical evidence and routine practice pragmatism for exercise as an antidepressant treatment

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Running head: Exercise works for depression

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Abstract:

In a previous commentary we have discussed some potential sources of heterogeneity of the antidepressant effects of exercise in people with depression, and provided suggestions on how to explore them in order to promote a broader understanding of the topic. These sources of heterogeneity were discussed focussing on the PICOS criteria referred to participants, interventions, comparisons, outcomes, and study designs. In response, Drs. Legrand and Neffs raised the discussion on 1) whether different symptomatology is able to moderate the antidepressant effects of exercise; 2) what is the "optimal dose" of exercise, which includes discussion on how to identify it, how to identify its biological correlates and how to shape exercise interventions, and 3) the necessity and validity of pragmatic RCTs. In the present manuscript, we have clarified and further expanded the points raised by Drs. Legrand and Neff.

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We would like to thank Drs Legrand and Neff for their interest in our paper, in which we discussed how the scientific community could advance further to understand the antidepressant role of exercise for individuals with depression, investigating potential sources of heterogeneities on the outcomes (1). Drs Legrand and Neff raised several interesting points and we are grateful for the opportunity to respond (2). Their points related to our suggestions that (a) different subtypes of depression (and other biological, clinical, psychological, social characteristics) may moderate the antidepressant effects of exercise; (b) designing exercise interventions should take into account the putative biological mediators involved; and (c) more pragmatic randomized controlled trials (RCTs) are needed due their "high external validity (outcome generalizability) by virtue of methodological features that are more closely aligned with 'real life' practice norms." Here, we wish to clarify and briefly expand on these points.

First, we suggested that, since depression exhibits heterogeneous symptomatology and biopsychosocial correlates, it is reasonable to assume that this heterogeneity will likely influence the effects of exercise on individuals with depression. Drs Legrand and Neff argued that the source we cited to support this point *"is presented as a review article about the 'moderators of response in exercise treatment or depression,' but it actually included a very small number of studies (n = 11), and some of the presented conclusions have been drawn on the basis of one single study."* We would like to clarify that our point primarily reflected a theoretical postulate, namely that *"patients with similar scores on measures of depression may experience dissimilar symptoms... This heterogeneity in symptoms may reflect differences in underlying neurobiological processes..., suggesting that the same exercise prescription may be less effective for some patients and more effective for others"* (p. 2)(3). Related to this postulate, we cited a review as providing *"initial evidence"* suggesting that *"clinical (severity of somatic symptoms), biological [brain derived neurotrophic factor, (BDNF) and tumor necrosis factor- α], psychological (self-esteem and life satisfaction), and social factors (support and marital status) may moderate the antidepressant effects of exercise"* (p. 2). We thus concur that conclusive evidence supporting our point is still lacking. In fact, we stated that, in the future, researchers can *"conduct moderator analyses to identify depressed subgroups with symptomatology and biopsychosocial characteristics associated with differential responses to exercise interventions,"* in order to test this assumption. Interestingly, since the publication of our initial paper, a study by Rethorst et al. (4) identified that patients with atypical depression are more likely to respond to exercise compared to patients with melancholic depression. Clearly, more research on this issue is needed.

Secondly, Drs Legrand and Neff raised three points pertaining to our discussion of the challenges involved in identifying the "optimal dose" of exercise. a) Their first point was that

"the majority of trials that used exercise (aerobic or anaerobic) in the management of clinical depression did not quantify physical activity in terms of energy expenditure (expressed in kilocalories/week) but rather in terms of time spent at various relative intensities." While it is true that most reports specify the prescribed dose of exercise in terms of intensity and duration (e.g., percentage of maximal aerobic capacity for intensity and number of minutes per session for duration), this approach is essentially interchangeable with describing exercise prescriptions in terms of energy expenditure (e.g., kcal per week), once body mass is taken into account (see p. 176 of the ACSM Guidelines for Exercise Testing and Prescription, 9th edition(5)). b) The second point made by Drs Legrand and Neff was that they do not "think that any method employed in quantifying the prescribed 'dose' of physical activity will help in identifying the biological mechanisms through which exercise decreases depression." We should clarify that we did not state that using a certain dose of exercise could provide information regarding the potential biological mechanisms. Our point was that the exercise prescription should be designed to take advantage of the postulated mechanisms underlying the antidepressant effect. For example, to promote the upregulation of Brain-Derived Neurotrophic Factor (BDNF), as one of the biological mechanisms accounting for the antidepressant effects of exercise (6), researchers should consider the evidence on the types and doses of exercise that optimize this effect. Specifically, optimizing BDNF upregulation seems to require low-intensity exercise (7). Furthermore, voluntary, self-paced exercise appears to be more effective than imposed exercise (8) and may prolong the elevation of BDNF (9). Moreover, in humans, the endocannabinoid anandamide in plasma has been found to be correlated with BDNF (10). Since anandamide is closely related to affective responses to exercise (11), these findings suggest that, to upregulate BDNF and stimulate neuroplasticity, an exercise stimulus may be required that (perhaps above all else) is experienced as pleasant. Thus, it should be apparent that an exercise prescription designed to optimize the antidepressant effect may be substantially different from a typical prescription, the purpose of which has traditionally been the promotion of adaptations in the cardiovascular system. c) The third point raised by Drs Legrand and Neff was that "it is doubtful that an exercise prescription can be shaped to target a specific 'putative mechanism of the antidepressant effects of exercise'." In support of this argument, they cited the study by Schmolesky et al. (2013)(12), which found no difference between "moderate" (60% heart rate reserve) or "vigorous" (80% heart rate reserve) and "short" (20 minutes) or "long" (40 minutes) exercise conditions in serum levels of BDNF in healthy men. However, Schmolesky et al. acknowledged that the increase in BDNF was highest in their lowest-intensity and shortest-duration group, albeit the difference was not statistically significant due to the low level of statistical power (see p. 507, also see their Figure 1C). Moreover, it should be noted that both intensities employed in the

study by Schmolesky et al. (i.e., 60% and 80% of heart rate reserve) are considered "hard/vigorous" by the American College of Sports Medicine (this range is defined as 60-84% of oxygen uptake or heart rate reserve, or 77-93% of maximal heart rate)(5).

The fourth point by Drs Legrand and Neff was related to our proposal for more pragmatic RCTs that replicate routine practice conditions. Instead, Drs Legrand and Neff argued that "what seems mostly needed is to develop RCTs conducted with a high degree of internal validity." First, although internal and external validity are usually reciprocally related, it is erroneous to think of them as necessarily antithetical, fundamentally incompatible, or mutually exclusive. Instead, the challenge is to maintain balance between the two (13). Also, exercise has shown established antidepressant efficacy under optimal-(clinical) conditions (i.e., with select and highly motivated participants, expertly administered treatments, etc) because both large clinical RCTs and meta-analyses have repeatedly provided relevant clinical evidence (14). What is currently set into question, in our view, is the antidepressant effectiveness of exercise in routine practice given the lack of pragmatic RCTs (15). Thus, the next step is to explore how clinical evidence can be translated into a pragmatic rationale for routine practice. In particular, how exercise guidelines for depression-3 times/week for a period of 12 to 14 weeks - (13) can be efficiently conducted under or adapted (and updated) to non-optimal conditions, specifically, pragmatic conditions that routine practice is daily faced with. These conditions include diverse and referred-instead of homogenous and exclusively voluntary-samples, increased difficulties in compliance due to psychosocial and environmental barriers commonly seen in daily life, non-expertly administered treatments, and untailored or incompatible exercise facilities and involved milieu to the needs of depressed people.

In this vein, RCTs with pragmatic design can make a real difference in people living with depression, especially since they measure effectiveness which is defined as "the benefit the treatment produces in routine practice" (16). To this extent, pragmatic RCTs are based on externally valid methodological criteria; recruitment of heterogeneous samples via patients' presentation and wide inclusion criteria, assessment on functional outcomes (17), acceptance of non-blinded therapists/patients (18), and suitability to compare usual to new treatments (19). Hence, pragmatic trials provide routine practice with direct evidence attributable to increased external validity. This is of major importance as the treatment of depression is realised mainly in primary care.

To the best of our knowledge, there has been only one pragmatic exercise RCT for people with depression (20). Trialists found a statistically significant large antidepressant effect-size (ES) for preferred intensity exercise vs. prescribed intensity exercise implemented three times per week for a period of four weeks. This finding becomes more important in light of the facts

that: i) exercise guidelines for depression recommend 12-14 weeks of exercising (13), and ii) pragmatic RCTs tend to reveal small ESs for the intervention (21) attributable, among other reasons, to the large standard deviation of the primary outcome of interest (e.g., depression) resulting from the lack of exclusion criteria in terms of severity (e.g., cut off point).

Drs Legrand and Neff have also raised a fifth point, underling that outcomes of pragmatic RCTs are not confound free. Indeed, pragmatic RCTs present increased risk of bias caused by confounding variables when comparable to trials conducted in a more homogeneous scenario. This risk, however, could be decreased when pragmatic RCTs are theory-driven and some of the previously identified confound factors are evaluated or controlled. For example, in the pragmatic RCT by Callaghan et al (2011)(20), both the intervention and the control groups received social support enforcement and, moreover, both groups showed comparable improvement in levels of social support at discharge. Thus, social support cannot be necessarily seen as a confounding factor in this trial.

Building the bridge between clinical evidence and routine practice pragmatism for exercise as an antidepressant treatment, preferred intensity exercise appears to be “fitting well” into routine practice.

In sum, we thank Drs Legrand and Neff for raising these interesting points. In many ways, we share similar views, common research findings, and the desire to utilize exercise as a treatment for people with depression. We hope that the clinical evidence that has demonstrated the antidepressant impact of exercise in robust RCTs (20, 22) and meta-analyses (14, 23, 24) can soon translate into broad changes in routine practice within emerging stepped-care collaborative approaches to treatment. We maintain that pragmatic RCTs will be a vital next step in bridging clinical evidence to routine practice pragmatism.

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